14 July 2022
EMA/COMP/605337/2022
Human Medicines Division

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 14-16 June 2022

Chair: Violeta Stoyanova-Beninska – Vice-Chair: Armando Magrelli

Health and safety information

In accordance with the Agency's health and safety policy, delegates were briefed on health, safety and emergency information and procedures prior to the start of the meeting.

Disclaimers

Some of the information contained in the minutes is considered commercially confidential or sensitive and therefore not disclosed. With regard to intended therapeutic indications or procedure scopes listed against products, it must be noted that these may not reflect the full wording proposed by applicants and may also vary during the course of the review. Additional details on some of these procedures will be published in the COMP meeting reports once the procedures are finalised.

Of note, this minutes are a working document primarily designed for COMP members and the work the Committee undertakes.

Note on access to documents

Some documents mentioned in the minutes cannot be released at present following a request for access to documents within the framework of Regulation (EC) No 1049/2001 as they are subject to on-going procedures for which a final decision has not yet been adopted. They will become public when adopted or considered public according to the principles stated in the Agency policy on access to documents (EMA/127362/2006).

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1. Introduction

1.1. Welcome and declarations of interest of members and experts

The Chair opened the meeting by welcoming all participants. Due to the current coronavirus (COVID-19) pandemic, and the associated EMA Business Continuity Plan (BCP), the meeting was held in-person with some members connected remotely (hybrid setting).

In accordance with the Agency's policy on handling of declarations of interests of scientific Committees' members and experts, based on the declarations of interest submitted by the Committee members and experts and based on the topics in the agenda of the meeting, the Committee Secretariat announced the restricted involvement of some Committee members for concerned agenda topics.

Participants were asked to declare any changes, omissions or errors to their declared interests concerning the matters for discussion. No new or additional interests or restrictions were declared. Restrictions applicable to this meeting are captured in the List of participants included in the minutes. Discussions, deliberations and voting took place in full respect of the restricted involvement of Committee members and experts in line with the relevant provisions of the Rules of Procedure and as included in the list of participants. All decisions taken at this meeting were made in the presence of a quorum of members. All decisions, recommendations and advice were agreed by consensus, unless otherwise specified.

1.2. Adoption of agenda

COMP agenda for 14-16 June 2022 was adopted with no amendments.

1.3. Adoption of the minutes

COMP minutes for 10-12 May 2022 were adopted with amendments and will be published on the EMA website.

2. Applications for orphan medicinal product designation

2.1. For opinion

2.1.1. - EMA/OD/0000073118

Treatment of perinatal asphyxia

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Intention to diagnose, prevent or treat

To establish correctly whether there exists a scientific rationale for the development of the proposed product for treatment of perinatal asphyxia the sponsor should further elaborate on:

- the relevance of the non-clinical model used for the treatment of perinatal asphyxia, and the interpretation of the results obtained in the experiments,

- the methodology used in the non-clinical studies as well as the results from these studies and its relevance for the development of the product in the condition.

In the written response, and during an oral explanation before the Committee on 14 June 2022, the sponsor provided responses which indicated that one of the substances on its own could have neuroprotective effects at the lower dose. The effect of the other substance in perinatal asphyxia was accepted by the COMP. The committee, however, was of the opinion that the response did not adequately establish the independent effect of the proposed substance and thus the additive effect of the proposed product. During the oral explanation it became apparent that the sponsor had conducted separate studies using only one substance in the treatment of perinatal asphyxia but that this data had not been submitted to the COMP. As the discussion turned to the existence of this data and studies conducted by the sponsor which were not published or available in the submission it became clear that the original submission was incomplete. As the data with one substance as well as unpublished combination data were not available for assessment, the COMP informed the sponsor that they could not give an opinion at the time of the oral explanation.

It was also not entirely clear if one of the substances was considered an excipient by the sponsor or an active substance. In case of an excipient the orphan application would have to be for the proposed substance alone.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 15 June 2022, prior to final opinion.

2.1.2. - EMA/OD/0000076399

Treatment of fracture nonunion (FNU)

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Intention to diagnose, prevent or treat

Fracture nonunion was asked to be justified as a distinct medical entity or a valid subset. Note that this is for the purposes of orphan medicinal product designation; the sponsor's attention was drawn to the Orphan regulations and relevant guidelines (especially section A of ENTR/6283/00).

To establish correctly whether the proposed condition as applied for is a valid subset for designation, the sponsor was also invited to elaborate on why the product might not work outside of the proposed subset, in particular with regards to long-bone fractures and prolonged healing fractures.

- Number of people affected

For the estimation and presentation of the prevalence estimate the sponsor was advised to refer to the "Points to Consider on the Estimation and Reporting of a Prevalence of a Condition for Orphan Designation".

The calculation of the prevalence was based on the assumption of 2 years duration of the condition. In addition, the sponsor calculated the annual rate and not the point prevalence.

The sponsor was requested to re-calculate and provide the point prevalence estimate (and not the annual rate) based on relevant epidemiological studies and registers for the proposed orphan condition. Given the uncertainties about the duration of the condition

which could extent 2 years in many patients, and the percentage of non-union among all fractures is reported to be as high as 5-10%, the sponsor was also requested to perform a sensitivity analysis of the reported calculations.

However, the acceptance of the estimation of the prevalence is subject to the agreement on the condition.

In the written response and during the oral explanation before the Committee on 14 June 2022, the sponsor proposed a prevalence of 3.79 based on the assumptions that the incidence is 1,894 FNU per 10.000 persons/year, the mean duration of FNU is 2 years and that the percentage of FNU among all fractures is 2.94. The COMP didn't conclude on the proposed estimate since that there is an overlap between delayed and nonunion fractures which affects also the calculation of the prevalence.

Regarding the significant benefit, the sponsor argued that FNUs are a subset of bone fractures and are characterised by unique pathophysiological features that distinguish FNUs from their parent condition (bone fracture) and other subsets of the parent condition (delayed union and malunion). Different pathophysiology of the four conditions is also reflected in different therapeutic approaches. Fractures are primarily treated by mechanical intervention only (fracture reduction and fixation). Malunions are treated by corrective osteotomy while delayed unions by conservative treatment or minimally invasive procedures aimed to accelerate the ongoing but slow healing without incremental risks. FNUs typically require open surgery with or without autologous bone grafting to ensure appropriate mechanical stability, initiate the bone formation cascade and eventually trigger FNU healing. Patients with FNUs can be therefore clearly differentiated from other bone fracture conditions, indicating that FNUs represent a valid subset for an orphan drug designation. However, the COMP considered that since the expected time of healing is not established, there is an overlap between delayed and non-union fracture which makes it difficult to distinct these two different subsets.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 14 June 2022, prior to final opinion.

2.1.3. *Salmonella enterica*, subsp. *enterica*, serovar Typhimurium, strain YS1646, live - EMA/OD/0000083166

Premier Research Group S.L.; Treatment of schwannoma

COMP Rapporteur: Bozenna Dembowska-Baginska

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Significant benefit

The arguments on significant benefit were based on an alternative mechanism of action and the potential improved efficacy in the condition. The COMP has noted that radiosurgery such as gamma knife is currently a satisfactory method in the treatment of schwannomas.

The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on the results from their non-clinical in vivo study to justify the assumption of significant benefit over radiosurgery.

In the written response, the sponsor provided answer to the question on significant benefit. They noted that currently there are no approved pharmacotherapies to treat schwannomas. Surgical resection and symptomatic management of pain are the current standards of care for schwannomas. Gamma knife radiosurgery (GKRS) has become an accepted treatment for vestibular schwannoma, with a high rate of tumour control and good clinical outcome in many patients (Fu et al., 2018). While helpful for many individuals (surgical resection is typically recommended for younger patients), surgery could often either fail to remove the entirety of the tumor(s) or fails to treat tumours that are associated with unacceptable operative risk as for example inability to perform operative resection due to location (e.g., brain stem associated, spinal cord associated) or number of tumors (Fehlings et al., 2016); or may have utility in conjunction with surgery and/ or GKRS. The sponsor has indicated that their product can be used in this treatment target group where there is an unmet need currently.

The COMP accepted that the non-clinical in vivo data submitted could be used to support the potential use in this patient population where surgery is not an option. The Committee was therefore of the opinion that they could recommend granting the orphan designation and cancelled the oral explanation.

Following review of the application by the Committee, it was agreed to rename the indication to treatment of schwannoma.

The Committee agreed that the condition, schwannoma, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing *Salmonella enterica*, subsp. *enterica*, serovar Typhimurium, strain YS1646, live was considered justified based on non-clinical in vivo data showing a reduction in tumour size.
The condition is chronically debilitating due to the development of central and peripheral nervous system tumours. The peripheral tumours usually affect vestibular and facial nerves leading to hearing loss, tinnitus, imbalance, facial weakness and facial paralysis. Long-term sequelae after surgery and malignant transformation into neurofibrosarcomas can also occur. The condition can be life-threatening due to compression of vital neurological structures in the brain stem, with the development of hydrocephalus and interference with respiratory functions.
The condition was estimated to be affecting approximately 0.2 in 10,000 persons in the European Union, at the time the application was made.
In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing *Salmonella enterica*, subsp. *enterica*, serovar Typhimurium, strain YS1646, live will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical in vivo data that demonstrate that the product could be used in patients where surgery is not an option. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for *Salmonella enterica*, subsp. *enterica*, serovar Typhimurium, strain YS1646, live, for treatment of schwannoma, was adopted by consensus.

2.1.4. - EMA/OD/0000083331

Treatment of Lambert-Eaton myasthenia syndrome (LEMS)

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor formally withdrew the application for orphan designation, on 18 May 2022, prior to responding to the list of issues.

2.1.5. - EMA/OD/0000084283

Treatment of pulmonary arterial hypertension

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Significant benefit

The argument on significant benefit is mainly based on the new mechanism of action and the potential improved efficacy in the condition, however, no data in support of this assumption has been provided. The clinical data referred to was not generated with the product proposed for designation and the sponsor has not sufficiently justified that an extrapolation can be done.

The significant benefit based on the non-clinical data should also be further justified as the sildenafil outcomes in some of the measurements were better than those obtained with the proposed product.

In the written response, and during an oral explanation before the Committee on 14 June 2022, the sponsor explained that in the non-clinical efficacy study, the sildenafil treatment group was included as the assay positive control group by the assay performer with the purpose of assay performance indicator. Sildenafil treatment group was not performed as an authorized product comparator for outcome comparison. As the assay positive control, sildenafil was used at a very high dose 25 mg/kg/day, around 4 folds higher than the clinical equivalent dose 20mg three times a day in human. Therefore, the sponsor was of the opinion that the results from the sildenafil treatment group with such high dose are not suitable for outcome comparison. The COMP did not agree as similar doses have been used in other non-clinical studies seen by the committee. As no further justification on the significant benefit was provided, the COMP was negative.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 14 June 2022, prior to final opinion.

2.1.6. - EMA/OD/0000077315

Treatment of type 1 diabetes (T1D) in DQ8 positive patients with residual beta cell function

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Condition

The validity of the proposed condition as a valid disease subset is questioned and should be further substantiated by the sponsor. Residual β-cell function is considered an early disease stage rather than a valid subset of T1D. Furthermore, DQ8 positivity indicates a higher genetic risk to develop T1D but it is questioned whether this is sufficient to justify a distinct disease subset from the whole T1D disease entity. The COMP considers that "treatment of

type 1 diabetes mellitus" is the most appropriate condition. Reference is made to the EC guideline ENTR/6283/00 Rev 5, p.6: https://ec.europa.eu/health/system/files/2021-12/2021-07_guideline_rev5_en.pdf

- Medical plausibility

The sponsor's clinical data is deemed insufficient to support medical plausibility due to the lack of a concomitant control and the short duration of the study. Especially in patients with a recent onset of insulin therapy, transient spontaneous remission can play a role in a significant number of patients and would also be expected to lead to improvement in HbA1c while maintaining similar doses of insulin therapy. The sponsor was requested to further substantiate the validity of the data to support medical plausibility.

Furthermore, the sponsor was asked to specify which of the two enantiomers of the proposed product is planned to be developed.

- Number of people affected

The validity of the proposed condition subset has been questioned by the COMP. The prevalence calculation and estimate will have to be in line with the final accepted condition.

- Significant benefit

The sponsor was asked to discuss significant benefit vs the authorized therapies in T1D and substantiate their claim with data.

In the written response, and during an oral explanation before the Committee on 14 June 2022, the main controversial issue remained the proposed condition wording "Treatment of type 1 diabetes in DQ8 positive patients with residual beta cell function". The presence of "residual beta cell function" was considered to be a disease stage in type 1 diabetes and is as such not a valid disease subset for the purpose of defining an orphan condition/condition subset.

Furthermore, the COMP was of the opinion that the claim for specific effects of the proposed product in DQ8 positive patients vs DR3-DQ2 positive patients should have been better substantiated with relevant pre-clinical or clinical data. Relative efficacy/activity data would be expected to support the proposed orphan condition subset with regards to DR4-DQ8 positivity. Therefore, overall, the proposed condition was not supported by COMP.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 15 June 2022, prior to final opinion.

2.1.7. - EMA/OD/0000083873

Treatment of choroideremia

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor formally withdrew the application for orphan designation, on 26 May 2022, prior to responding to the list of issues.

2.1.8. - EMA/OD/0000083791

Treatment of multiple myeloma

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Significant benefit

The sponsor was requested to further discuss the significant benefit over Abecma (and potentially Carvykti). The proposed claim on an improved safety was not sufficiently justified and restricted on only one type of adverse events (cytokine release syndrome). No information was found on the baseline characteristics of the patient population treated with the proposed product. The sponsor was asked to discuss the limitations of the indirect comparison with respect to safety, also with respect to the target population (and the treatment schedule). The "wider target patient population" should be further explained by the sponsor. Alternative claims for significant benefit can also be put forward.

In the written response, and during an oral explanation before the Committee on 15 June 2022, the sponsor submitted a comparison of the baseline patient characteristics between the population enrolled on their study and the populations enrolled to the pivotal studies, KarMMa (Abecma SmPC) supporting the approval of Abecma under a conditional marketing authorization (CMA) and CARTITUDE-1 supporting the CHMP positive opinion of a CMA for Carvykti (Berdeja, 2021). It was considered, both by the sponsor and the COMP, that the populations in the patient populations in their study vs KarMMa and CARTITUDE-1 were not sufficiently comparable and the results were too immature to allow conclusions with respect to the criterion of significant benefit over Abecma and Carvykti.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 15 June 2022, prior to final opinion.

2.1.9. - EMA/OD/0000079201

Treatment of non-infectious intermediate, posterior and chronic anterior uveitis

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Number of people affected

For the estimation and presentation of the prevalence estimate the sponsor was advised to refer to the "Points to Consider on the Estimation and Reporting of a Prevalence of a Condition for Orphan Designation".

The sponsor was requested to justify the inclusion/choice of the sources selected for the estimation of the prevalence of the condition. The sponsor was asked to describe and justify the methodology used for the prevalence calculation.

- Significant benefit

The arguments on significant benefit were based on an alternative formulation of the proposed product which could deliver a similar level of efficacy to other currently authorised immunomodulating and anti-inflammatory agents' and the potential improved efficacy in the condition. There was no pertinent discussion regarding any presumed significant benefit of topical nanocapsule formulation of the proposed product to other products currently authorised in the European Community for use in the intended orphan condition. The sponsor was thus requested to further discuss exhaustively all arguments that would justify the notion of significant benefit over all centrally and nationally approved

immunomodulating and anti-inflammatory agents with a therapeutic indication in non-infectious uveitis (NIU), or any broader therapeutic indication that would overlap with NIU.

The sponsor was requested to further elaborate on the results from their non-clinical in vivo study to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan condition.

The sponsor was asked to detail the results of any clinical data to support the significant benefit assumption in the context of the current therapeutic management of patients.

In the written response, the sponsor provided a clarification regarding the questions on prevalence and significant benefit. The COMP accepted the revised methodology for the prevalence estimate as well as the final conclusion that 3.5 in 10,000 persons were estimated to have the condition in Europe. The written response regarding significant benefit was however insufficient.

During an oral explanation before the Committee on 15 June 2022, the sponsor only provided hypothetical explanations regarding significant benefit. No new data was submitted to support the claim that their product would be of a clinically relevant advantage in the treatment of anterior non-infectious uveitis. The sponsor acknowledged that there was the limited data they had submitted initially was insufficient to support this claim and that at this time they did not have any additional data which could help. The COMP was therefore of the opinion that it could not recommend granting the orphan designation.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 16 June 2022, prior to final opinion.

2.1.10. thiostrepton - EMA/OD/0000079978

EMA Regulatory Submissions Expediter Limited; Treatment of malignant mesothelioma

COMP Rapporteur: Bozenna Dembowska-Baginska

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Significant benefit

The arguments on significant benefit were based only on the new mechanism of action. The sponsor was requested to further discuss the arguments provided for significant benefit and to provide indirect comparisons versus the authorised medicinal products in order to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan condition.

In the written response, the sponsor provided further explanation to the question by the COMP.

The sponsor argued that none of the approved therapies can invoke remission rates high enough for quantification. Additional clinical data was provided from a case report of a MM patient who treated with thiostrepton and revealed a partial response (PR) and decrease in tumour size.

In addition, the sponsor argued that preclinical cell-based studies in human mesothelioma cell lines showed that thiostrepton can kill 90% of cells at 10 µM or less, compared to 20-35% killing by cisplatin at 10 µM and 30-75% killing by pemetrexed at 200 µM (Nelson,

2021; Papazoglou, 2019). Combining cisplatin (10 μM) and pemetrexed (200μM) kills 50-75% of cells, significantly less than the 90% of cells killed consistently by thiostrepton treatment (Papazoglou, 2019; Nelson, 2021). Cisplatin, pemetrexed, and the combination of both therapies consistently yield suboptimal efficacy (50% reduction in mesothelioma cell viability for each agent alone, and 50-75% reduction in combination) in other mesothelioma cell lines (Vandermeers, 2009). Finally in vivo data showed that thiostrepton treatment via intraperitoneal injection at a dose of 50 mg/kg three times weekly yielded a 70% reduction in tumour volume (Cunniff, 2015). In syngeneic mesothelioma murine models, nivolumab had no effect on tumour growth or survival (Fear, 2018). Ipilimumab reduced tumour growth by 50% (Fear, 2018). Cisplatin and pemetrexed have negligible efficacy in xenograft and syngeneic murine models (Vandermeers, 2009). Based on this data the COMP concluded that preclinical data support superiority of thiostrepton treatment of mesothelioma compared to the available data using approved mesothelioma treatments. However, the COMP recommended that protocol assistance is sought prior to submission of the application for marketing authorisation, particularly with regard to the clinical development and the data that will be required for the demonstration of significant benefit.

The COMP considered the written response adequately addressed the question raised and cancelled the oral explanation.

The Committee agreed that the condition, malignant mesothelioma, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing thiostrepton was considered justified based on in vivo non-clinical data which showed reduced tumour volume in a xenograft model of the condition.

The condition is life-threatening due to the invasion of the pleura leading to pleural effusions, dyspnoea and malignant ascites. Patients with pleural mesothelioma usually die due to increasing tumour bulk that gradually fills the hemithorax causing progressive respiratory compromise pneumonia, or myocardial dysfunction with arrhythmias. In patients with peritoneal mesothelioma, distension due to ascites, abdominal pain, and organ impairment such as bowel obstruction are observed.

The condition was estimated to be affecting less than 1 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing thiostrepton will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data showing higher anti-tumour effects compared to authorised medicinal products. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for thiostrepton for treatment of malignant mesothelioma, was adopted by consensus.

2.1.11. - EMA/OD/0000080896

Treatment of Prader-Willi syndrome

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor formally withdrew the application for orphan designation, on 20 May 2022, prior to responding to the list of issues.

2.1.12. - EMA/OD/0000083574

Treatment of West syndrome

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor formally withdrew the application for orphan designation, on 24 May 2022, prior to responding to the list of issues.

2.1.13. - EMA/OD/0000083982

Treatment of cutaneous T-cell lymphoma (CTCL)

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Intention to diagnose, prevent or treat

To establish correctly whether there exists a scientific rationale for the development of the proposed product for treatment of cutaneous T-cell lymphoma, the sponsor was requested to provide any in vivo data on the proposed condition. In addition, the sponsor was invited to provide a discussion on the impact of the product on the progression of the disease.

- Significant benefit

The arguments on significant benefit were based on the new mechanism of action and the potential improved efficacy in the condition. However, comparison with available treatments of CTCL were lacking.

The sponsor was invited to further elaborate on the assumption of significant benefit over authorised medicinal products for the proposed orphan condition, and to provide indirect or direct comparative data.

In the written response and during an oral explanation before the Committee on 14 June 2022, the sponsor defended their position. It could be agreed with the sponsor the limitations of the current approaches for managing patients with the condition and the novelty of the proposed approach. However, there is presently no justification as to why the proposed product should provide significant benefit to cutaneous T-cell lymphoma patients compared to the authorized treatments. The assumption of medical plausibility and significant benefit should be substantiated by data showing that the proposed product might provide benefit in CTCL patients. However, available data aiming to show that the proposed product may work are not mature enough to endorse the rationale in the context of the applied condition. As a result, the question remained as to what degree a positive effect would translate into a clinically and meaningful beneficial effect for the patient. The COMP concluded that the presented evidence is not sufficient to support an orphan designation.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 15 June 2022, prior to final opinion.

2.1.14. heterologous swine glyco-humanised polyclonal antibody against T lymphocytes - EMA/OD/0000083254

Xenothera; treatment in solid organ transplantation

COMP Rapporteur: Frauke Naumann-Winter

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Intention to diagnose, prevent or treat

Prevention of graft rejection following solid organ transplantation should be justified as a distinct medical entity or a valid subset. Note that this is for the purposes of orphan medicinal product designation; the sponsor's attention is drawn to the Orphan regulations and relevant guidelines (especially section A of ENTR/6283/00). The sponsor was advised by the committee to change the condition to treatment in solid organ transplantation.

- Significant benefit

The arguments on significant benefit were based on an alternative mechanism of action and the potential improved efficacy and safety in the condition. An alternative mechanism of action alone is not considered acceptable to justify significant benefit. The sponsor was requested to further discuss the arguments provided for significant benefit and to justify the lack of data from non-clinical models in the setting of solid organ transplantation

The sponsor should further elaborate on the characteristics and clinical outcome of all patients who had renal transplants and received the proposed product as induction therapy to support the significant benefit assumption in the context of the current therapeutic management of patients.

In the written response, the sponsor agreed to change the condition to treatment in solid organ transplantation. The sponsor also further justified the suitability of their non-clinical in vivo models. The skin graft model was selected because it is the most sensitive model and provides a quick response. Skin transplantation has been already used to test several potential immunosuppressive strategies, including antilymphocyte globulin (Préville et al, 2001; Kobayashi et al, 1972).

The sponsor presented efficacy data from the recently completed study on 10 kidney-transplanted patients who received the proposed product as induction therapy on top of standard maintenance therapy. No graft loss was observed after a 3-months follow-up. Pharmacokinetic data suggest a persisting mild non-depleting immunosuppressive effect due to a relatively high half-life of 34 days. The clinical trial was performed in patients who would not be candidates for T-cell depletion according to the guideline so that the favourable outcome cannot be fully attributed to the proposed product. No graft loss in patients was observed after a 3 month follow-up. The preliminary clinical data and the justification of the relevance of the non-clinical in vivo allograft model for the proposed condition was considered sufficient to support significant benefit.

The COMP was of the opinion that it could recommend granting the orphan designation and the oral explanation was cancelled.

Following review of the application by the Committee, it was agreed to rename the indication to treatment in solid organ transplantation.

The Committee agreed that the condition, solid organ transplantation, is a distinct medical entity and meets the criteria for orphan designation

The intention to treat the condition with the medicinal product containing Heterologous swine glyco-humanised polyclonal antibody against T lymphocytes was considered justified based on non-clinical in vivo data in relevant models for the condition showing a reduction in the rejection of allogeneic grafts.

The condition is chronically debilitating and life threatening due to delayed graft function following transplantation and graft loss.

The population of patients eligible for treatment of the condition was estimated to be approximately 0.5 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing Heterologous swine glyco-humanised polyclonal antibody against T lymphocytes will be of significant benefit to the population at risk of developing the condition. The sponsor has provided non-clinical in vivo data that show a reduction in allogeneic graft rejection compared to standard of care. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for heterologous swine glyco-humanised polyclonal antibody against T lymphocytes, for treatment in solid organ transplantation, was adopted by consensus.

2.1.15. - EMA/OD/0000075761

Treatment of mantle cell lymphoma (MCL)

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Significant benefit

The sponsor was asked to further discuss the arguments provided for significant benefit over temsirolimus and Tecartus, authorised in the EU for the treatment of adult patients with MCL.

In the written response, and during an oral explanation before the Committee on 15 June 2022 the sponsor defended their position. It could be agreed with the sponsor the existing limitations of the current approaches for managing patients with the condition specially as the condition progresses to more advanced stages. However, there is presently no convincing data as to why the proposed product should provide significant benefit to patients with mantle cell lymphoma compared to other authorized treatments including CAR-T cells. The COMP concluded that the presented evidence is not sufficient and remains yet immature to support an orphan designation.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 16 June 2022, prior to final opinion.

2.1.16. hydroquinidine hydrochloride - EMA/OD/0000080688

Teofarma S.r.l.; Treatment of Brugada syndrome (BrS)

COMP Rapporteur: Zsofia Gyulai

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Number of people affected

For the estimation and presentation of the prevalence estimate the sponsor was advised to refer to the "Points to Consider on the Estimation and Reporting of a Prevalence of a Condition for Orphan Designation".

The sponsor proposed a prevalence of 1.61 however they mentioned a publication (Gourraud et al., 2016) which refers to a prevalence of 5 per 10,000 persons. This should be further discussed. In addition, the sponsor should re-calculate the prevalence with all patients with Brugada syndrome and not only the patients regarded as "at risk" (type I ECG).

- Significant benefit

The sponsor argued that there are no medicines authorised for the proposed condition.

However, since there are medicinal products authorised for malignant arrhythmias, the sponsor was asked to provide indirect comparisons with the proposed product versus the products authorised for malignant arrhythmias. In addition, the sponsor was requested to discuss the significant benefit versus the current standard of care.

In the written response, the sponsor provided further explanation to the question by the COMP.

Regarding the calculation of the prevalence the sponsor argued that only a type 1 ST-segment elevation is considered as diagnostic of BrS. Type 2 usually prompts the performance of a pharmacological test with a sodium channel blocker and, if the test is positive (i.e., the appearance of a type 1 pattern), the subjects are considered as patients affected by BrS but at such a low risk that only regular ECG controls are recommended. Type 3 has no clinical significance and is not regarded as true BrS. Therefore, the only group of patients whose prevalence in Europe is relevant to the present application is the one showing a spontaneous Type 1 pattern. The calculated prevalence for this group of patients is 0.92 per 10.000 persons. The COMP agreed with the revised prevalence and concluded that a prevalence of approximately 1 can be accepted.

For the justification of the significant benefit the sponsor argued that patients who qualify for an implantable cardioverter defibrillator (ICD) but present a contraindication to the ICD or refuse it can be treated with hydroquinidine. In comparison to quinidine in a study by Chimienti et al. (1988), hydroquinidine was found to be more potent than quinidine since it was used in a lower dose (808 mg of hydroquinidine base versus 990 mg of quinidine base). The study concluded that hydroquinidine has stronger antiarrhythmic activity than quinidine and so may be used in lower doses; it is effective with plasma concentrations lower than those of quinidine. The COMP agreed that hydroquinidine showed reduction in ventricular arrhythmia in patients who do not benefit from the existing available therapeutic treatments. This can justify the significant benefit for the orphan designation.

The COMP considered the written response adequately addressed the question raised and cancelled the oral explanation.

The Committee agreed that the condition, Brugada syndrome is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing hydroquinidine hydrochloride was considered justified based on preliminary clinical data which reduced ventricular arrhythmia in patients with Brugada syndrome who were treated with the proposed product.

The condition is chronically debilitating due to palpitations, syncope, seizures, and ventricular tachycardia and life-threatening due to ventricular fibrillation resulting in sudden death.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing hydroquinidine hydrochloride will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data which showed reduction in ventricular arrhythmia in patients who may not benefit from the existing available therapeutic options. The Committee considered that this constitutes a clinically relevant advantage.

The condition was estimated to be affecting approximately 1 in 10,000 persons in the European Union, at the time the application was made.

A positive opinion for hydroquinidine hydrochloride, for treatment of Brugada syndrome, was adopted by consensus.

2.1.17. - EMA/OD/0000083246

Treatment of pulmonary arterial hypertension

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Significant benefit

The sponsor was requested to detail the results of any clinical or non-clinical data to support the significant benefit assumption of the fixed dose proposed combination product over the mono-component products. In the absence of such data the significant benefit cannot be established.

In the written response and during the oral explanation before the Committee on 16 June 2022, the sponsor maintained that providing the proposed combination product as 1 fixed-dose tablet rather than 3 single tablets results in additional benefit for the patients because it reduces the overall pill burden, thereby addressing one of the well-recognized issues that results in suboptimal adherence to treatment. For the purpose of orphan designation an improved adherence and reduction in medication errors could per se not be considered a significant benefit, as it would have to result in a better outcome for the patients in e.g. better efficacy or improved safety as compared to the loose combination and there is at this stage no evidence that this is the case. A reduced pill burden based on a change from three to one table a day in patients already on a high pill burden could not be considered self-evident and therefore not support by the COMP.

In communicating the outcome of the discussion to the sponsor, the sponsor formally withdrew the application for orphan designation on 15 June 2022, prior to the adoption of the final opinion.

2.1.18. - EMA/OD/0000082229

Treatment of GM1 gangliosidosis

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor formally withdrew the application for orphan designation, on 17 May 2022, prior to responding to the list of issues.

2.2. For discussion / preparation for an opinion

2.2.1. Humanised IgG4 monoclonal antibody against active complement component 1, subcomponent s - EMA/OD/0000021158

Genzyme Europe B.V.; Treatment of autoimmune haemolytic anaemia

COMP Rapporteur: Karri Penttila

The Committee agreed that the condition, autoimmune haemolytic anaemia, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing 'humanised IgG4 monoclonal antibody against active complement component 1, subcomponent s' was considered justified based on preliminary efficacy data demonstrating decreased haemolysis and increased haemoglobin levels.

The condition is chronically debilitating due to venous or arterial thrombotic events, infections, requirement of red blood cell transfusion and decreased quality of life.

The condition was estimated to be affecting less than 2.6 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing 'humanised IgG4 monoclonal antibody against active complement component 1, subcomponent s' will be of significant benefit to those affected by the condition. The sponsor has provided early clinical data from persons affected by cold autoimmune haemolytic anaemia that demonstrate sustained inhibition of haemolysis and improvement in haemoglobin levels following a single administration with the product. The effect of the treatment compares favourably to the authorised treatments. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for humanised IgG4 monoclonal antibody against active complement component 1, subcomponent s, for treatment of autoimmune haemolytic anaemia, was adopted by consensus.

2.2.2. - EMA/OD/0000073417

Treatment of CTLA-4 haploinsufficiency with autoimmune infiltration disease

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the July 2022 meeting.

2.2.3. fosmanogepix - EMA/OD/0000076464

Pfizer Europe MA EEIG; Treatment of invasive candidiasis

COMP Rapporteur: Olimpia Neagu

The Committee agreed that the condition, invasive candidiasis, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing fosmanogepix was considered justified based on non-clinical data showing effect in models of the condition, and preliminary clinical data showing clinically meaningful treatment success rate and improved survival in patients who received the proposed product.

The condition is life-threatening with above 50% mortality in the acute phase in Intensive Care Units.

The condition was estimated to be affecting approximately 0.5 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing fosmanogepix will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate treatment success in patients who are unable to receive antifungal treatment available to date due to resistance, contraindication, intolerance, and/or lack of clinical response. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for fosmanogepix, for treatment of invasive candidiasis, was adopted by consensus.

2.2.4. - EMA/OD/0000076480

Treatment of myasthenia gravis

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the July 2022 meeting.

2.2.5. fosmanogepix - EMA/OD/0000076916

Pfizer Europe MA EEIG; Treatment of invasive aspergillosis

COMP Rapporteur: Olimpia Neagu

The Committee agreed that the condition, invasive aspergillosis, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing fosmanogepix was considered justified based on non-clinical studies showing clearance of Aspergillus spp infection and improved survival in valid models of the condition, and preliminary clinical data showing meaningful improved survival in patients who received the proposed product.

The condition is life-threatening and chronically debilitating due to progressive dyspnoea, chest pain, haemoptysis, and dissemination of the infection to several organs including the brain. Mortality rates are up to 70–95% in recipients of bone marrow transplant.

The population of patients eligible for the treatment of the condition was estimated to be less than 2 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing fosmanogepix will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate improved survival in patients who are unable to receive standard of care antifungal therapy due to lack of clinical response or anticipated resistance. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for fosmanogepix, for treatment of invasive aspergillosis, was adopted by consensus.

2.2.6. - EMA/OD/0000077279

Treatment of retinopathy of prematurity

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the July 2022 meeting.

2.2.7. mRNA encoding modified human ornithine transcarbamylase - EMA/OD/0000077782

Arcturus Therapeutics Europe B.V.; Treatment of ornithine transcarbamylase deficiency

COMP Rapporteur: Darius Matusevicius

The Committee agreed that the condition, ornithine transcarbamylase deficiency, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing mRNA encoding modified human ornithine transcarbamylase was considered justified based on non-clinical data demonstrating a dose-dependent improved plasma glutamine and ammonia biomarkers, and extended survival.

The condition is chronically debilitating and life threatening due to the consequences of metabolic decompensation leading to developmental delay, mental disability, and other types of neurological damage.

The condition was estimated to be affecting approximately 0.1 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing mRNA encoding modified human ornithine transcarbamylase will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data in a relevant model of the condition demonstrating restoration of functional ornithine transcarbamylase, and improved survival which cannot be achieved with currently

authorised products. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for mRNA encoding modified human ornithine transcarbamylase, for treatment of ornithine transcarbamylase deficiency, was adopted by consensus.

2.2.8. autologous naive regulatory T cells transduced with a lentiviral vector encoding for a chimeric antigen receptor to recognise the HLA-A*02 antigen - EMA/OD/0000078610

Sangamo Therapeutics France S.A.S.; Treatment in solid organ transplantation

COMP Rapporteur: Frauke Naumann-Winter

The Committee agreed that the condition, solid organ transplantation, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing autologous naive regulatory T cells transduced with a lentiviral vector encoding for a chimeric antigen receptor to recognise the HLA-A*02 antigen was considered justified based on non-clinical data in relevant models for the condition showing a reduction in graft-versus-host disease scores and increased graft survival.

The condition is chronically debilitating and life threatening due to delayed graft function following transplantation, graft loss and about 50% of patients retaining a functional organ after 10 years.

The condition was estimated to be affecting approximately 0.6 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing autologous naive regulatory T cells transduced with a lentiviral vector encoding for a chimeric antigen receptor to recognise the HLA-A*02 antigen will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data that demonstrate the induction of a cellular-mediated immunomodulatory environment within the allograft upon treatment which has the potential to reduce long term use of immunosuppressive therapy. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for autologous naive regulatory T cells transduced with a lentiviral vector encoding for a chimeric antigen receptor to recognise the HLA-A*02 antigen, for treatment in solid organ transplantation, was adopted by consensus.

2.2.9. odronextamab - EMA/OD/0000080170

Regeneron Ireland Designated Activity Company; Treatment of follicular lymphoma

COMP Rapporteur: Maria Elisabeth Kalland

The Committee agreed that the condition, follicular lymphoma, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing odronextamab was considered justified based on preliminary clinical data which showed responses in patients with relapsed or refractory follicular lymphoma.

The condition is life-threatening and chronically debilitating due to lymphadenopathy, splenomegaly, bone marrow dysfunction, and the potential of transformation to aggressive lymphoma.

The condition was estimated to be affecting approximately 4.9 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing odronextamab will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that showed complete responses in a high proportion of previously treated patients with relapsed or refractory follicular lymphoma who have failed several lines of approved therapies. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for odronextamab, for treatment of follicular lymphoma, was adopted by consensus.

2.2.10. zilucoplan - EMA/OD/0000080529

UCB Pharma; Treatment of myasthenia gravis

COMP Rapporteur: Darius Matusevicius

The Committee agreed that the condition, myasthenia gravis, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing zilucoplan was considered justified based on clinical data showing positive responses on myasthenia gravis specific outcome measures in patients affected by the condition.

The condition is chronically debilitating due to muscle weakness affecting in particular muscles that control eye and eyelid movement, facial expressions, chewing, talking, and swallowing and life-threatening due to respiratory impairment.

The condition was estimated to be affecting approximately 2 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing zilucoplan will be of significant benefit to those affected by the condition. The sponsor has provided clinical data showing positive responses on myasthenia gravis specific outcome measures in a broader population including non-refractory generalized myasthenia gravis which is not covered by the authorized product. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for zilucoplan, for treatment of myasthenia gravis, was adopted by consensus.

2.2.11. 3-(1,3-benzodioxol-5-yl)-5-(3-bromophenyl)-1H-pyrazole - EMA/OD/0000081208

Teva B.V.; Treatment of multiple system atrophy

COMP Rapporteur: Zsofia Gyulai

The Committee agreed that the condition, multiple system atrophy, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing 3-(1,3-benzodioxol-5-yl)-5-(3-bromophenyl)-1H-pyrazole was considered justified based on non-clinical data which shows improved histological features and motor-function manifestations in a valid model of the condition.

The condition is chronically debilitating due to progressive motor and/or cerebellar dysfunction, autonomic failure, and gait disorders, and life threatening due to recurrent infections or pulmonary embolism.

The condition was estimated to be affecting approximately 0.4 in 10,000 persons in the European Union, at the time the application was made.

The sponsor has also established that there exists no satisfactory method of treatment in the European Union for patients affected by the condition.

A positive opinion for 3-(1,3-benzodioxol-5-yl)-5-(3-bromophenyl)-1H-pyrazole, for treatment of multiple system atrophy, was adopted by consensus.

2.2.12. efgartigimod alfa - EMA/OD/0000082060

Argenx; Treatment of pemphigus

COMP Rapporteur: Armando Magrelli

The Committee agreed that the condition, pemphigus, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing efgartigimod alfa was considered justified based on preliminary clinical data in patients with the condition showing complete response in treated patients via the activity score of the pemphigus Disease Area Index.

The condition is chronically debilitating and potentially life threatening due to chronic blistering associated with dehydration and secondary infection which can lead to premature death.

The condition was estimated to be affecting approximately 3 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing efgartigimod alfa will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate a reduction in the use of corticosteroid therapy in patients who received the sponsor's product. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for efgartigimod alfa, for treatment of pemphigus, was adopted by consensus.

2.2.13. (S)-1-(4-(1-(3,4,5-trimethoxyphenyl)-1H-imidazol-4-ylamino)thieno[2,3-d]pyrimidin-2-yl)pyrrolidine-2-carboxamide - EMA/OD/0000082579

Biocryst Ireland Limited; Treatment of fibrodysplasia ossificans progressiva

COMP Rapporteur: Ingeborg Barisic

The Committee agreed that the condition, fibrodysplasia ossificans progressiva, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing (S)-1-(4-(1-(3,4,5-trimethoxyphenyl)-1H-imidazol-4-ylamino)thieno[2,3-d]pyrimidin-2-yl)pyrrolidine-2-carboxamide was considered justified based on non-clinical data in models of the condition showing reduction in heterotopic ossification.

The condition is chronically debilitating due to episodes of painful tumour-like soft-tissue swellings followed by the development of extra bone throughout the body and across joints causing progressive impairment of movement. The condition is life-threatening due to complications of thoracic insufficiency syndrome as a consequence of ankyloses in the thorax that lead to premature death around 50 years of age.

The condition was estimated to be affecting less than 0.01 in 10,000 persons in the European Union, at the time the application was made.

The sponsor has also established that there exists no satisfactory method of treatment in the European Union for patients affected by the condition.

A positive opinion for (S)-1-(4-(1-(3,4,5-trimethoxyphenyl)-1H-imidazol-4-ylamino)thieno[2,3-d]pyrimidin-2-yl)pyrrolidine-2-carboxamide, for treatment of fibrodysplasia ossificans progressiva, was adopted by consensus.

2.2.14. berzosertib - EMA/OD/0000082615

Merck Europe B.V.; Treatment of small-cell lung cancer

COMP Rapporteurs: Enrico Costa, Brigitte Schwarzer-Daum

The Committee agreed that the condition, small-cell lung cancer, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing berzosertib was considered justified based on preliminary clinical data showing responses in relapsed or refractory small cell lung cancer patients.

The condition is chronically debilitating and life threatening due to its rapid progression and the development of widespread metastases, with a poor 5-years overall survival.

The condition was estimated to be affecting approximately 1.2 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing berzosertib will be of significant benefit to those affected by

the condition. The sponsor has provided preliminary clinical data that demonstrate responses for the combination of the proposed product with topotecan in relapsed or refractory small cell lung cancer patients and in a broader indication not covered by the authorised treatments. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for berzosertib, for treatment of small-cell lung cancer, was adopted by consensus.

2.2.15. odronextamab - EMA/OD/0000083083

Regeneron Ireland Designated Activity Company; Treatment of diffuse large B-cell lymphoma

COMP Rapporteurs: Jana Mazelova, Frauke Naumann-Winter

The Committee agreed that the condition, diffuse large B-cell lymphoma, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing odronextamab was considered justified based on preliminary clinical data showing durable responses achieved in patients with relapsed/refractory diffuse large B-cell lymphoma.

The condition is chronically debilitating due to involvement of single or multiple nodal or extranodal sites, including the gastrointestinal tract, the central nervous system and bone marrow and life-threatening in patients with relapsed/refractory disease.

The condition was estimated to be affecting approximately 4.3 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing odronextamab will be of significant benefit to those affected by the condition. The sponsor has provided clinical data which demonstrated durable responses in heavily pre-treated patients with relapsed/refractory diffuse large B-cell lymphoma. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for odronextamab, for treatment of diffuse large B-cell lymphoma, was adopted by consensus.

2.2.16. parsaclisib - EMA/OD/0000083733

Incyte Biosciences Distribution B.V.; Treatment of autoimmune haemolytic anaemia

COMP Rapporteurs: Enrico Costa, Karri Penttila

The Committee agreed that the condition, autoimmune haemolytic anaemia, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing parsaclisib was considered justified based on preliminary clinical data which suggest that treatment with parsaclisib leads to an increase in haemoglobin levels.

The condition is chronically debilitating due to venous or arterial thrombotic events, infections, requirement of red blood cell transfusions and decreased quality of life.

The condition was estimated to be affecting approximately 2.6 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing parsaclisib will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data which suggest that treatment with parsaclisib leads to an increase in haemoglobin levels in patients insufficiently controlled with previous first- and/or second-line therapies. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for parsaclisib, for treatment of autoimmune haemolytic anaemia, was adopted by consensus.

2.2.17. panobinostat - EMA/OD/0000085141

Scendea (NL) B.V.; Treatment of glioma

COMP Rapporteur: Brigitte Schwarzer-Daum

The Committee agreed that the condition, glioma, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing panobinostat was considered justified based on non-clinical studies in a valid model of the condition showing prolonged survival as well as preliminary clinical data, in patients with diffuse intrinsic pontine glioma responding to treatment.

The condition is debilitating due to symptoms caused the tumour compressing the surrounding brain tissue including headache, anorexia, nausea, vomiting, seizures, neurological deficits, personality changes and cognitive decline. The condition is also life-threatening, with poor 5-year survival of less than 5% for glioblastoma grade 4 patients.

The condition was estimated to be affecting approximately 2.8 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing panobinostat will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that patients with diffuse intrinsic pontine glioma, treated with the product, can survive longer than otherwise expected when treated with standard of care (based on indirect comparison to literature data). The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for panobinostat, for treatment of glioma, was adopted by consensus.

2.2.18. 2,4,6,7,8,9-hexahydro-4-((2-methylphenyl)methyl)-7-(phenylmethyl)imidazo(1,2-a)pyrido(3,4-e)pyrimidin-5(1H)-one - EMA/OD/0000085459

Chimerix IRL Limited; Treatment of glioma

COMP Rapporteur: Dinko Vitezic

The Committee agreed that the condition, glioma, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing 2,4,6,7,8,9-hexahydro-4-((2-methylphenyl)methyl)-7-(phenylmethyl)imidazo(1,2-a)pyrido(3,4-e)pyrimidin-5(1H)-one was considered justified based on non-clinical data demonstrating antitumor effects, and on preliminary clinical data showing tumour regression and improved survival in patients affected by the condition treated with the proposed product as single agent.

The condition is debilitating due to symptoms caused the tumour compressing the surrounding brain tissue including headache, anorexia, nausea, vomiting, seizures, neurological deficits, personality changes and cognitive decline. The condition is also life-threatening, with poor 5-year survival of less than 5% for glioblastoma grade 4 patients.

The condition was estimated to be affecting approximately 2.6 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing 2,4,6,7,8,9-hexahydro-4-((2-methylphenyl)methyl)-7-(phenylmethyl)imidazo(1,2-a)pyrido(3,4-e)pyrimidin-5(1H)-one will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate effects in relapse patients previously treated with temozolomide and/or radiotherapy. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 2,4,6,7,8,9-hexahydro-4-((2-methylphenyl)methyl)-7-(phenylmethyl)imidazo(1,2-a)pyrido(3,4-e)pyrimidin-5(1H)-one, for treatment of glioma, was adopted by consensus.

2.2.19. vilobelimab - EMA/OD/0000085590

InflaRx GmbH; Treatment of pyoderma gangrenosum

COMP Rapporteur: Bozenna Dembowska-Baginska

The Committee agreed that the condition, pyoderma gangrenosum, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing vilobelimab was considered justified based on preliminary clinical data which showed clinical remission with ulcer closure.

The condition is chronically debilitating and life-threatening due to severe pain, infections and purulent ulcerations.

The condition was estimated to be affecting approximately 0.6 in 10,000 persons in the European Union, at the time the application was made.

The sponsor has also established that there exists no satisfactory method of treatment in the European Union for patients affected by the condition.

A positive opinion for vilobelimab, for treatment of pyoderma gangrenosum, was adopted by consensus.

2.2.20. - EMA/OD/0000085640

Treatment of Covid-19 and dengue co-infection

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the July 2022 meeting.

[Post-meeting note: The sponsor formally withdrew the application for orphan designation, on 24 June 2022.]

2.2.21. sodium phenylbutyrate - EMA/OD/0000085676

Renantos Pharmavertriebsgesellschaft mbH; Treatment of maple syrup urine disease

COMP Rapporteur: Geraldine O'Dea

The Committee agreed that the condition, maple syrup urine disease, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing sodium phenylbutyrate was considered justified based on positive observations on clinically relevant biomarkers both in the context of chronic, and acute attack management of the condition.

The condition is chronically debilitating due to psychomotor delay and life-threatening in particular due to decompensation episodes leading to progressive encephalopathy and cerebral oedema.

The condition was estimated to be affecting less than 0.1 in 10,000 persons in the European Union, at the time the application was made.

The sponsor has also established that there exists no satisfactory method of treatment in the European Union for patients affected by the condition.

A positive opinion for sodium phenylbutyrate, for treatment of maple syrup urine disease, was adopted by consensus.

2.2.22. human decorin fused to the truncated homing peptide CRK - EMA/OD/0000085783

Tampereen Korkeakoulusäätiö Sr; Treatment of epidermolysis bullosa

COMP Rapporteur: Gloria Maria Palomo Carrasco

The Committee agreed that the condition, epidermolysis bullosa, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing human decorin fused to the truncated homing peptide CRK was considered justified based on non-clinical data in a relevant model of the condition, showing prolonged survival and reduced fibrosis.

The condition is chronically debilitating and life-threatening due to blister formation following minor friction or trauma, leading to the development of multiple complications including life-threatening infections, failure to thrive, and predisposition to the development of squamous cell carcinoma.

The condition was estimated to be affecting approximately 0.6 in 10,000 persons in the European Union, at the time the application was made.

The sponsor has also established that there exists no satisfactory method of treatment in the European Union for patients affected by the condition.

A positive opinion for human decorin fused to the truncated homing peptide CRK, for treatment of epidermolysis bullosa, was adopted by consensus.

2.2.23. - EMA/OD/0000085805

Treatment of mastocytosis

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the July 2022 meeting.

2.2.24. - EMA/OD/0000085890

Treatment of idiopathic hypersomnia

The COMP adopted a list of issues that will be sent to the sponsor. The Committee will discuss the submitted answers to the list of issues at the July 2022 meeting.

2.2.25. pyridoxal 5'-phosphate - EMA/OD/0000085913

Amsterdam UMC; Treatment of pyridoxal 5'-phosphate homeostasis protein deficiency

COMP Rapporteur: Giuseppe Capovilla

Following review of the application by the Committee, it was agreed to rename the indication to treatment of pyridoxal 5'-phosphate homeostasis protein deficiency.

The Committee agreed that the condition, pyridoxal 5'-phosphate homeostasis protein deficiency, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing pyridoxal 5'-phosphate was considered justified based on clinical data showing patients can become seizure free after treatment.

The condition is life-threatening and chronically debilitating due to intractable seizures which can lead to sudden unexpected death in epilepsy.

The condition was estimated to be affecting approximately 0.001 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing pyridoxal phosphate will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate a reduction in seizures in patients who were refractory to antiseizure medication. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for pyridoxal 5'-phosphate, for treatment of pyridoxal 5'-phosphate homeostasis protein deficiency, was adopted by consensus.

2.2.26. W253R/R275S tissue plasminogen activator - EMA/OD/0000086046

Op2Lysis; Treatment of non-traumatic spontaneous intracerebral haemorrhage

COMP Rapporteur: Michel Hoffmann

Following review of the application by the Committee, it was agreed to rename the indication to treatment of non-traumatic spontaneous intracerebral haemorrhage.

The Committee agreed that the condition, non-traumatic spontaneous intracerebral haemorrhage, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing W253R/R275S tissue plasminogen activator was considered justified based on preliminary non-clinical in vivo data showing neurological recovery.

The condition is life-threatening due to a high mortality which reaches approximately 50% within the first 3 months and most survivors are left with severe neurological disabilities.

The condition was estimated to be affecting approximately 2.8 in 10,000 persons in the European Union, at the time the application was made.

The sponsor has also established that there exists no satisfactory method of treatment in the European Union for patients affected by the condition.

A positive opinion for W253R/R275S tissue plasminogen activator, for treatment of non-traumatic spontaneous intracerebral haemorrhage, was adopted by consensus.

2.2.27. liraglutide - EMA/OD/0000086049

Pietro Maffei; Treatment of Wolfram syndrome

COMP Rapporteur: Vallo Tillmann

The Committee agreed that the condition, Wolfram syndrome, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing liraglutide was considered justified based on non-clinical data in valid models showing the delayed onset of diabetes and preventing the axonal degeneration and retinal ganglion cell death, as well as preliminary clinical data showing an improvement in C-peptide levels and diminishing the progression of neuro-ophthalmological and neurophysiological disease parameters.

The condition is life-threatening with a life-expectancy of 30 years and chronically debilitating due to the development of diabetes mellitus and optic nerve atrophy.

The condition was estimated to be affecting approximately 0.2 in 10,000 persons in the European Union, at the time the application was made.

The sponsor has also established that there exists no satisfactory method of treatment in the European Union for patients affected by the condition.

A positive opinion for liraglutide, for treatment of Wolfram syndrome, was adopted by consensus.

2.2.28. - EMA/OD/0000086052

Treatment of Alstrom syndrome

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the July 2022 meeting.

2.2.29. - EMA/OD/0000086055

Treatment of Bardet-Biedl syndrome

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the July 2022 meeting.

2.2.30. erlotinib - EMA/OD/0000086361

Imagine Institut Des Maladies Genetiques Necker Enfants Malades; Treatment of pachyonychia congenita

COMP Rapporteur: Lyubina Racheva Todorova

The Committee agreed that the condition, pachyonychia congenita, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing erlotinib was considered justified based on two clinical cases showing that the proposed product was able to improve plantar keratoderma of patients affected by the condition.

The condition is chronically debilitating due to impaired ambulation associated with plantar keratoderma, blistering and pain.

The condition was estimated to be affecting approximately 0.01 in 10,000 persons in the European Union, at the time the application was made.

The sponsor has also established that there exists no satisfactory method of treatment in the European Union for patients affected by the condition.

A positive opinion for erlotinib, for treatment of pachyonychia congenita, was adopted by consensus.

2.2.31. toripalimab - EMA/OD/0000086527

TMC Pharma (EU) Limited; Treatment of nasopharyngeal cancer

COMP Rapporteurs: Jana Mazelova, Bozenna Dembowska-Baginska

The Committee agreed that the condition, nasopharyngeal cancer, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing toripalimab was considered justified based on the responses observed in preliminary clinical data.

The condition is chronically debilitating due to epistaxis, obstruction of the nasopharynx, hearing impairment and tinnitus, headache, diplopia, facial pain and numbness or paresthesia and life-threatening due to reduced survival.

The condition was estimated to be affecting approximately 0.7 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing toripalimab will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate improvement in

progression-free-survival and overall survival with addition of the product to current standard of care, as well as responses in subjects with advanced relapsed and/or metastatic nasopharyngeal cancer who had received prior systemic therapy. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for toripalimab, for treatment of nasopharyngeal cancer, was adopted by consensus.

2.2.32. - EMA/OD/0000086562

Prevention of acute liver failure

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the July 2022 meeting.

2.2.33. - EMA/OD/0000086580

Treatment of graft-versus-host-disease

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the July 2022 meeting.

2.2.34. (R)-3-(2,3-dihydroxypropyl)-6-fluoro-5-(2-fluoro-4-iodophenylamino)-8-methylpyrido[2,3-d]pyrimidine-4,7(3H,8H)-dione - EMA/OD/0000086748

Diamond Pharma Services Ireland Limited; Treatment of familial adenomatous polyposis

COMP Rapporteur: Armando Magrelli

The Committee agreed that the condition, familial adenomatous polyposis, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing (R)-3-(2,3-dihydroxypropyl)-6-fluoro-5-(2-fluoro-4-iodophenylamino)-8-methylpyrido[2,3-d]pyrimidine-4,7(3H,8H)-dione was considered justified based on non-clinical in vivo data showing reduced polyp counts and decreased dysplasia severity.

The condition is chronically debilitating and life threatening due to the high risk of developing colorectal cancer as well as extra colonic manifestations which include polyps of the gastric fundus and duodenum, desmoids, gastric and duodenal carcinoma, follicular or papillary thyroid cancer, and central nervous system tumours.

The condition was estimated to be occurring in approximately 0.6 in 10,000 persons in the European Union, at the time the application was made.

The sponsor has also established that there exists no satisfactory method of treatment in the European Union for patients affected by the condition.

A positive opinion for (R)-3-(2,3-dihydroxypropyl)-6-fluoro-5-(2-fluoro-4-iodophenylamino)-8-methylpyrido[2,3-d]pyrimidine-4,7(3H,8H)-dione, for treatment of familial adenomatous polyposis, was adopted by consensus.

2.3. Revision of the COMP opinions

None

2.4. Amendment of existing orphan designations

None

2.5. Appeal

None

2.6. Nominations

2.6.1. New applications for orphan medicinal product designation - Appointment of COMP rapporteurs

COMP rapporteurs were appointed for 33 applications.

2.7. Evaluation on-going

1 application for orphan designation will not be discussed as evaluation is ongoing.

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

3.1.1. -

Treatment of pancreatic cancer

The Committee was briefed on the significant benefit issues. The COMP adopted the proposed answers on the significant benefit issues.

3.1.2. -

Treatment of mucopolysaccharidosis II (Hunter's syndrome)

The Committee was briefed on the significant benefit issues. The COMP adopted the proposed answers on the significant benefit issues via written procedure.

3.1.3. -

Treatment of acute myeloid leukaemia

The Committee was briefed on the significant benefit issues. The COMP adopted the proposed answers on the significant benefit issues.

3.1.4. -

Treatment of myelofibrosis

The Committee was briefed on the significant benefit issues. The COMP adopted the proposed answers on the significant benefit issues.

3.2. Finalised letters

3.2.1. -

Treatment of multiple myeloma

The finalised letter was circulated for information.

3.2.2. -

Treatment of primary biliary cholangitis

The finalised letter was circulated for information.

3.2.3. -

Treatment of myelodysplastic syndromes

The finalised letter was circulated for information.

3.3. New requests

None

4. Review of orphan designation for orphan medicinal products at time of initial marketing authorisation

4.1. Orphan designated products for which CHMP opinions have been adopted

None

4.2. Orphan designated products for discussion prior to adoption of CHMP opinion

4.2.1. – fosdenopterin - EMEA/H/C/005378/0000, EU/3/10/777, EMA/OD/0000074822

Accelerated assessment

Comharsa Life Sciences Ltd; Treatment of molybdenum cofactor deficiency type A

The status of the procedure at CHMP was noted.

4.2.2. - valoctocogene roxaparvovec - EMEA/H/C/005830/0000, EU/3/16/1622, EMA/OD/0000067127

BioMarin International Limited; Treatment of haemophilia A

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the July 2022 meeting.

4.2.3. Vyvgart - efgartigimod alfa - EMEA/H/C/005849/0000, EU/3/18/1992, EMA/OD/0000083237

Argenx; Treatment of myasthenia gravis

COMP Rapporteurs: Elisabeth Penninga; Cécile DopAn opinion recommending not to remove Vyvgart, efgartigimod alfa, EU/3/18/1992 from the EC Register of Orphan Medicinal Products was adopted by consensus.

The orphan maintenance assessment report will be publicly available on the EMA website.

[Post-meeting note: The COMP adopted the opinion by written procedure following its June meeting.]

4.2.4. Crysvita - burosumab - EMEA/H/C/004275/II/0023, EU/3/18/2011, EMA/OD/0000051257

Kyowa Kirin Holdings B.V.; Treatment of phosphaturic mesenchymal tumour

CHMP Rapporteur: Kristina Dunder; CHMP Co-Rapporteur: Jayne CroweAn opinion recommending not to remove Crysvita, burosumab, EU/3/18/2011 from the EC Register of Orphan Medicinal Products was adopted by consensus.

The orphan maintenance assessment report will be publicly available on the EMA website.

[Post-meeting note: The COMP adopted the opinion by written procedure following its June meeting.]

4.2.5. - asciminib - EMEA/H/C/005605/0000, EU/3/20/2261, EMA/OD/0000068920

Novartis Europharm Limited; Treatment of chronic myeloid leukaemia

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the July 2022 meeting.

4.2.6. - maribavir - EMEA/H/C/005787/0000

Takeda Pharmaceuticals International AG Ireland Branch

a) Treatment of cytomegalovirus disease in patients with impaired cell mediated immunity, EU/3/13/1133, EMA/OD/0000091101

The status of the procedure at CHMP was noted.

b) Prevention of cytomegalovirus disease in patients with impaired cell mediated immunity deemed at risk, EU/3/07/519, EMA/OD/0000091090

The status of the procedure at CHMP was noted.

4.2.7. Pepaxti - melphalan flufenamide - EMEA/H/C/005681/0000, EU/3/15/1463, EMA/OD/0000063986

Oncopeptides AB; Treatment of plasma cell myeloma

COMP Rapporteurs: Karri Penttila; Elisabeth Johanne Rook

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the July 2022 meeting.

[Post-meeting note: The sponsor formally withdrew the application for orphan designation on 22 June 2022.]

The orphan designation withdrawal assessment report will be publicly available on the EMA website.

4.2.8. Tecartus - brexucabtagene autoleucel - EMEA/H/C/005102/II/0008/G, EU/3/20/2344, EMA/OD/0000063560

Kite Pharma EU B.V.; Treatment of acute lymphoblastic leukaemia

CHMP Rapporteur: Jan Mueller-Berghaus

The COMP adopted a list of issues that will be sent to the sponsor. The Committee will discuss the submitted answers to the list of issues at the July 2022 meeting.

4.2.9. - vutrisiran - EMEA/H/C/005852/0000, EU/3/18/2026, EMA/OD/0000085855

Alnylam Netherlands B.V.; Treatment of transthyretin-mediated amyloidosis

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the July 2022 meeting.

4.2.10. - teclistamab - EMEA/H/C/005865/0000, EU/3/20/2331, EMA/OD/0000083072

Accelerated assessment

Janssen-Cilag International; Treatment of multiple myeloma

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the July 2022 meeting.

4.3. Appeal

None

4.4. On-going procedures

COMP co-ordinators were appointed for 4 applications.

4.5. Orphan Maintenance Reports

Documents were tabled for information.

5. Review of orphan designation for authorised orphan medicinal products at time marketing authorisation extension

5.1. After adoption of CHMP opinion

None

5.2. Prior to adoption of CHMP opinion

None

5.3. Appeal

None

5.4. On-going procedures

None

6. Application of Article 8(2) of the Orphan Regulation

None

7. Organisational, regulatory and methodological matters

7.1. Mandate and organisation of the COMP

7.1.1. COMP membership

None

7.1.2. Vote by proxy

Dinko Vitezic gave a proxy to Martin Mozina to vote on behalf of Dinko Vitezic during part of the June 2022 COMP meeting.

Giuseppe Capovilla gave a proxy to Armando Magrelli to vote on behalf of Giuseppe Capovilla during the June 2022 COMP meeting.

7.1.3. Strategic Review & Learning meetings

None

7.1.4. Protocol Assistance Working Group (PAWG)

The working group on Protocol Assistance met remotely on 10 June 2022 at 14:00.

7.1.5. Principal Decisions Database

None

7.2. Coordination with EMA Scientific Committees or CMDh-v

7.2.1. Recommendation on eligibility to PRIME – report

Documents were tabled for information

7.3. Coordination with EMA Working Parties/Working Groups/Drafting Groups

7.3.1. Working Party with Patients' and Consumers' Organisations (PCWP)

Documents were tabled for information

7.3.2. Working Party with Healthcare Professionals' Organisations (HCPWP)

Documents were tabled for information

7.4. Cooperation within the EU regulatory network

7.4.1. European Commission

None

7.5. Cooperation with International Regulators

7.5.1. Food and Drug Administration (FDA)

None

7.5.2. Japanese Pharmaceuticals and Medical Devices Agency (PMDA)

None

7.5.3. Therapeutic Goods Administration (TGA), Australia

None

7.5.4. Health Canada

None

7.6. Contacts of the COMP with external parties and interaction with the Interested Parties to the Committee

None

7.7. COMP work plan

None

7.8. Planning and reporting

7.8.1. List of all applications submitted/expected and the COMP rapporteurship distribution of valid applications submitted in 2022

An updated list of all applications submitted/expected and the COMP rapporteurship distribution of valid applications submitted in 2022 were circulated.

7.8.2. Overview of orphan marketing authorisations/applications

An updated overview of orphan applications for Marketing Authorisation was circulated.

8. Any other business

8.1. EMA Business Pipeline activity and Horizon scanning

The document was tabled for information.

9. List of participants

including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 14-16 June 2022 meeting.

Name	Role	Member State or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Violeta Stoyanova-Beninska	Chair	Netherlands	No interests declared	
Armando Magrelli	Member (Vice-Chair)	Expert recommended by EMA	No interests declared	
Brigitte Schwarzer-Daum	Member	Austria	No restrictions applicable to this meeting	
Tim Leest	Member	Belgium	No interests declared	
Lyubina Racheva Todorova	Member	Bulgaria	No interests declared	
Dinko Vitezic	Member	Croatia	No interests declared	
Elli Loizidou	Member	Cyprus	No interests declared	
Jana Mazelova	Member	Czechia	No interests declared	
Elisabeth Penninga	Member	Denmark	No interests declared	
Vallo Tillmann	Member	Estonia	No interests declared	
Karri Penttilä	Member	Finland	No interests declared	
Cecile Dop	Member	France	No restrictions applicable to this meeting	
Frauke Naumann-Winter	Member	Germany	No interests declared	

Name	Role	Member State or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Vasileios Papadopoulos	Member	Greece	No interests declared	
Zsofia Gyulai	Member	Hungary	No interests declared	
Geraldine O'Dea	Member	Ireland	No interests declared	
Enrico Costa	Member	Italy	No interests declared	
Irena Rogovska	Member	Latvia	No restrictions applicable to this meeting	
Aušra Matulevičienė	Member	Lithuania	No interests declared	
Michel Hoffmann	Member	Luxembourg	No interests declared	
Robert Nistico	Member	Malta	No restrictions applicable to this meeting	
Elisabeth Johanne Rook	Member	Netherlands	No interests declared	
Maria Elisabeth Kalland	Member	Norway	No interests declared	
Bożenna Dembowska-Bagińska	Member	Poland	No restrictions applicable to this meeting	
Dinah Duarte	Member	Portugal	No interests declared	
Olimpia Neagu	Member	Romania	No interests declared	
Eva Malikova	Member	Slovak Republic	No interests declared	
Martin Mozina	Member	Slovenia	No interests declared	
Gloria Maria Palomo Carrasco	Member	Spain	No interests declared	
Darius Matusevicius	Member	Sweden	No restrictions applicable to this meeting	
Ines Alves	Member	Patients' organisation representative	No participation in discussion, final deliberations and voting on:	4.2.2. - valoctocogene roxaparvovec - EMEA/H/C/005830/0000, EU/3/16/1622, EMA/OD/0000067127 BioMarin International Limited;

Name	Role	Member State or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
				Treatment of haemophilia A
Maria Cavaller Bellaubi	Expert*	Patients' organisation representative	No restrictions applicable to this meeting	
João Rocha	Expert*	Portugal	No restrictions applicable to this meeting	
Meeting run with support from relevant EMA staff				

* Experts were evaluated against the agenda topics or activities they participated in.

10. Explanatory notes

The notes below give a brief explanation of the main sections and headings in the COMP agenda and should be read in conjunction with the agenda or the minutes.

Abbreviations / Acronyms

CHMP: Committee for Medicinal Product for Human Use

COMP: Committee for Orphan Medicinal Products

EC: European Commission

OD: Orphan Designation

PA: Protocol Assistance

PDCO: Paediatric Committee

PRAC: Pharmacovigilance and Risk Assessment Committee

SA: Scientific Advice

SAWP: Scientific Advice Working Party

Orphan Designation *(section 2 Applications for orphan medicinal product designation)*

The orphan designation is the appellation given to certain medicinal products under development that are intended to diagnose, prevent or treat rare conditions when they meet a pre-defined set of criteria foreseen in the legislation. Medicinal products which get the orphan status benefit from several incentives (fee reductions for regulatory procedures (including protocol assistance), national incentives for research and development, 10-year market exclusivity) aiming at stimulating the development and availability of treatments for patients suffering from rare diseases.

Orphan Designations are granted by Decisions of the European Commission based on opinions from the COMP. Orphan designated medicinal products are entered in the Community Register of Orphan Medicinal Products.

Protocol Assistance *(section 3 Requests for protocol assistance with significant benefit question)*

The protocol assistance is the help provided by the Agency to the sponsor of an orphan medicinal product, on the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of the medicinal product in view of the submission of an application for marketing authorisation.

Sponsor

Any legal or physical person, established in the Community, seeking to obtain or having obtained the designation of a medicinal product as an orphan medicinal product.

Maintenance of Orphan Designation *(section 4 Review of orphan designation for orphan medicinal products for marketing authorisation).*

At the time of marketing authorisation, the COMP will check if all criteria for orphan designation are still met. The designated orphan medicinal product should be removed from the Community Register of Orphan Medicinal Products if it is established that the criteria laid down in the legislation are no longer met.

More detailed information on the above terms can be found on the EMA website: www.ema.europa.eu/